EXPERIMENTAL STUDIES ON THE ETIOLOGY OF ACUTE PNEUMONITIS.*

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Introduction.

Acute exudative inflammation of the lungs may develop as a metastatic lesion secondary to disease processes in other parts of the body, or it may accompany acute interstitial processes arising usually from the pleura, or it may arise as a primary infection of the lung forming patchy bronchopneumonic or diffuse lobar lesions. The bacterial incitants of acute primary infectious processes in the lung are now well known. Our knowledge of the essential conditions which determine the extent and nature of the disease processes in the lung and elsewhere, however, lacks the precision which can come only from exact experimental data. This may be attained only when it is possible to reproduce at will the various disease processes in animals. With pneumococcus pneumonia this has not heretofore been satisfactorily accomplished. As a result of a long series of experiments, I have finally determined a method by which the diffuse lesions of pneumococcus pneumonia may readily be incited in the rabbit. This method it is the purpose of this paper to record; but the failures and successes of others have in such large measure contributed to my final results that they may with advantage be briefly considered. The significance of this previous work, however, may not be fully appreciated without summing up our knowledge of the distribution and disposal of bacteria in general in the respiratory apparatus, of the bacterial incitants of pneumonia, and of the paths of infection.

Bacteria of the Normal Respiratory Apparatus. Inspired foreign particles and bacteria, as shown by the researches of Arnold[3] and many others, are deposited chiefly on the moist surfaces of the upper respiratory passages, although they may occasionally be carried to the alveoli of the lung. For most bacteria the healthy mucous membrane is an unfavorable environment, yet this varies greatly in different parts of the tract and with different species of bacteria. In the *mouth* and *nares* bacteria are being constantly deposited on the mucous membranes. As indicated by the researches of Thomson and Hewlett,[178] Wright,[197] Nenninger,[131] Müller,[126] and Laschtschenko,[109] some of them disappear very rapidly; others may develop and exist as harmless parasites. These secretions thus contain many different species of micro-organisms, among which the bacteria commonly associated with pneumonia—the pneumococcus, streptococcus, staphylococcus, and the bacillus of Friedländer—have often been found. Suffice it to note that the pneumococcus was present in a large proportion of Sternberg's cases,[173] 20 per cent. of Fraenkel's cases,[67] 17 per cent. of Besser's cases,[17] 20 per cent. of Wolf's cases,[196] 30 per cent. of Bein's cases,[15] 55 per cent. of Miller's cases,[123] 4 per cent. of Neumann's normal cases,[136] and in 100 per cent. of the forty tonsils examined by Bezancon and Griffon.[20] Netter[132] divided his cases into those with and those without a history of pneumonia, and found the pneumococcus in four out of five and in one out of five cases, respectively, and he also claims to have found the organisms virulent five, ten, or more years after a pneumonic infection. Furthermore, it is significant to note that it has been experimentally shown by Guarnieri,[80] by Bordonni-Uffredozzi,[24] by Grawitz and Steffen,[77] by Spolverini,[170] and by Ottolenghi[138] that the pneumococcus in sputum may remain alive and virulent for two to four months.

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In the *trachea* bacteria are also deposited on the mucous membranes,* but under normal conditions these are comparatively few in number and are rapidly disposed of by the cilia, and also by the action of the mucus, which, in the researches of Wurtz and Lemoyez[193] with sputum, of Walthard,[187] of Stroganoff,[175] and of Morisani[124] with the uterine secretions, and more recently of Arloing[3] with pure mucus, has shown marked bactericidal qualities.† Examination of the human trachea at autopsy, as in the studies of Baumgarten,[10] Hoffmann,[91] v. Besser,[19] Ritchie,[153] Claisse,[38] and Durck,[45] has revealed the presence of micro-organisms in a considerable proportion of the cases, but the trachea and lung at autopsy, although of normal appearance, may not be considered to be under normal conditions. Normal conditions, it is evident, are more closely approximated in the researches conducted on animals, as in the studies of Hildebrandt,[89] Klipstein,[102] Gobell,[74] Rosenthal,[154] Beco,[12] Buttersack,[30] Boni,[23] Barthel,[9] and Calamida and Bertarelli.[31] In these examinations of the trachea of animals, bacteria have not often been found, and the lower portions of the trachea and the bronchi have thus been considered to be practically sterile.‡

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* As suggested by the researches of Slawjansky[167] and of Kuttner[107] with the injection of foreign substances, and of Pernici and Scagliosi[143] with the injection of bacteria into the general circulation, the possibility of bacteria being carried to and through the mucous membrane from the circulating blood may also be considered.

† In the experiments of Grawitz,[77] Steffen,[77 171] and also of Hopkins[92] this action of mucus was not detected in sputum sterilized by heat.

‡ In the course of my experiments, examination of the lower portion of the trachea clearly indicated that in the rabbit, at least, this portion of the respiratory tract is normally free from micro-organisms; but that contaminations, attributed very largely to the death agony, readily occur; and that the bacteria of such contaminations may grow so that, unless the animal be examined immediately after death, considerable numbers of bacteria may be found. Furthermore, animals dying of disease, when compared with those killed, frequently showed the presence of contaminating bacteria in this portion of the respiratory apparatus, although the entire tract was apparently normal.

In the normal *lung* bacteria do not, so far as is known, exist as harmless parasites. The researches of Prudden and Northrup,[144] Tschistovitch,[180] [181] Grammatschikoff,[76] Silfast,[163] and others show that pathogenic as well as non-pathogenic bacteria in the air spaces degenerate: some are taken up by the phagocytes and carried into the lymph channels; others are destroyed by the body fluids. By these processes considerable numbers of bacteria may be disposed of in a comparatively short time.

Bacterial Incitants of Pneumonia. The infectious nature of pneumonia was first definitely established by the researches of Friedländer,[71] Talamon,[176] and Fraenkel.[67] The various studies of the pneumonic lung at autopsy in long series of cases by many subsequent observers, notably, Weichselbaum,[190] Wolf,[196] Finkler,[62] Prudden and Northrup,[144] Kreibach,[105] Netter,[133] [135] Pearce,[141] Durck,[44] and Howard,[93] have served to indicate the etiological importance of the different bacterial incitants. The pneumococcus is now considered as practically the sole incitant of the diffuse lobar lesions. Netter believes the disease to be specific; others concede a small percentage of the lesions to the bacillus of Friedländer. In bronchopneumonia the more recent researches indicate that the pneumococcus rather than the streptococcus is more frequently the incitant, yet in the secondary lesions following certain of the exanthemata the streptococcus is still considered the more important.

Although the inflammatory reactions induced by the pneumococcus, streptococcus, staphylococcus, and pneumobacillus are somewhat similar, they differ in many respects, so that there are certain types of lesion more commonly associated with one species than with others. The pneumococcus lesions are in general more diffuse, œdematous, fibrinous, hemorrhagic, and less necrotic than those induced by either the streptococcus or pneumobacillus. In pneumococcus lesions gangrene rarely develops, except as the result of secondary infection; on the other hand, the pneumobacillus is not infrequently associated with such a condition. The pneumococcus and streptococcus are, on the whole, more similar in their pathogenic effects than any of the others; but in the lung the streptococcus rarely if ever gives rise to the lobar form of pneumonia. The staphylococcus processes are less variable, almost always circumscribed, rarely diffuse or fibrinous, as compared with those of the other three species.

These broad differences, to some extent dependent upon the virulence of the bacterial species, may be modified by many conditions, such as the age or susceptibility of the individual, and more particularly by the susceptibility of the race or species of animal infected. In respect to infection with the pneumococcus, Behring and Nissen,[14] Fraenkel,[67] Gamaleia,[72] Kruse and Pansini,[106] and many others have determined that mice and rabbits are the most susceptible; guinea-pigs, rats, squirrels, cats, dogs, sheep, horses, and man are in varying degrees less susceptible; and fowls more or less immune.

PATHS OF INFECTION IN PNEUMONIA. Infection through the air-passages is undoubtedly the rule in bronchopneumonia; but certain secondary pneumonias arising by hæmatogenous infection may so closely simulate bronchopneumonia that the rule must either be excepted for these cases or they must be classified with the metastatic pneumonias. Most observers believe that lobar pneumonia also develops from an infection through the air-passages; but regarding the universality of this there is some question, doubtless arising from the unsatisfactory results that have attended tracheal inoculations in animals and other similar experimental attempts to induce the lobar lesion. Two other paths of infection, the hæmatogenous and the lymphatic, have therefore been considered by some theoretically possible. As supporting hæmatogenous infection, the results of the blood examinations of pneumonia patients have been cited. Careful scrutiny of these, however,[*] reveals the fact that while bacteriæmia develops early as well as late in the disease, there is no indication that this is other than secondary to the local lesion. The occurrence of pneumonia in the fœtus offers the clearest example of hæmatogenous infection. Cases of such infection have been reported by Strachan,[174] Marchand,[117] Thorner,[179] Netter,[134] Viti,[184] Czmetscha,[41] and Delestre.[42] These reports, however, are in many respects inadequate; in some histological examinations of the lesions were not made, in others infection by the air-passages after birth could not be excluded. They, therefore, fail to establish the occurrence of lobar pneumonia from placental infection. Experimental support of hæmatogenous infection in lobar pneumonia is certainly very meagre, uncorroborated, and relatively insignificant. Finally, suffice it to note that, clinically as well as experimentally, pneumonic lesions of the lobar type are uncommon in races or individuals very susceptible to systemic pneumococcus infection and more common in resistant individuals or species in which systemic infections are less usual.

There are few facts to support a theory of lymphatic infection. Grober's[79] interesting work on the tonsil and its lymphatic connections is extremely significant as applied to tuberculous and pleural infections, but the plague bacillus is the only species which is definitely known to reach the lung through the cervical lymphatics and give rise to an acute exudative pneumonitis. These plague pneumonias, however, are of a peculiar metastatic lymphatic type, quite different from the lobar lesions.

In view of these facts and in the absence of reliable positive data, the possibility of lobar pneumonia arising by hæmatogenous or lymphatic infection must be considered as not yet established.*

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[*] Witness, for example, the studies of Guarnieri,[80] Fraenkel,[67] Banti,[8] Belfanti,[16] Sittmann,[166] Sello,[164] James and Tuttle,[95] Prochaska,[145] White,[192] Baduel,[7] Pane,[139] and Wandel,[189] many of which, and others not cited, have been reviewed recently by Ewing.[60]

PREVIOUS RESEARCHES ON EXPERIMENTAL PNEUMONIA.

The earliest attempts to induce pneumonia in animals, which were made when the disease was attributed to exposure or fatigue and before its infectious nature was determined, are now chiefly of historic interest. The first significant experiments comprised the inoculation of animals with the exudates and autopsy material from pneumonia cases. After the infectious nature of the disease had thus been established and the several bacteria concerned isolated and differentiated, greater scope and precision of experimentation became possible, pure cultures replaced the exudates, etc.; or if the exudates were used the bacteria contained in the exudates were previously determined, and special methods of inoculation were adopted. At first the lungs were inoculated through the chest-wall, then this rather crude method was discarded and the animals were forced by various contrivances to inhale the infectious material. Finally, tracheal injections of the infectious material were used. Although infection of the normal lung of various animal species were not infrequently secured by certain of these methods, typical diffuse pneumonic lesions rarely developed. Attention was therefore directed to the animal and attempts were made through injury to render the lung more susceptible to infection. The results of these experiments as regards the development of circumscribed bronchopneumonic types of lesions were more satisfactory and uniform; but as regards the development of diffuse lobar types of lesion were uncertain and far from satisfactory.

The experiments of former observers may, therefore, be divided into two main classes: those on normal and those on artificially predisposed animals.

PREVIOUS ATTEMPTS TO INDUCE PNEUMONIA BY INFECTION OF THE UNINJURED OR NORMAL LUNG. *Intravenous*, *subcutaneous*, *intraocular* inoculations—in short, all methods giving rise to a primary general infection, whether practised in the ordinary laboratory routine or in the hope of securing pneumonic lesions—have, with a few uncorroborated exceptions,† uniformly failed to give rise to the definite lesions of either bronchopneumonia or lobar pneumonia. *Intraperitoneal* inoculation has similarly failed, the few exceptional lesions being of the pleuropneumonic type.

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* This, however, does not exclude the possibility of a metastatic pneumonia, as has been exceptionally noted, simulating the diffuse lobar processes. In fact, between the more typical processes of all forms of acute exudative pneumonitis intermediate lesions occur which histologically are distinguished with difficulty.

† Schultz[163] reports pneumonic lesions in eight out of fourteen rabbits inoculated intravenously with pneumococci. Apparently the collapsed lungs were examined, and certainly the lesions found were inaccurately described as typically exudative. Klipstein[103] reports one instance of a diffuse pneumonia being found after subcutaneous inoculation with a colon bacillus, and Fraenkel[68] noted the exceptional development of pneumonic lesions after subcutaneous inoculation of the thorax with the pneumococcus. An early observer, Klebs,[100]

With *intrathoracic* inoculation the needle may or may not penetrate the lung; if the lung tissues are entered a local injury, with more or less hemorrhagic extravasation, results; if not, the pleural cavity only is inoculated and the infection of the lung is secondary, thus pleuropneumonia is incited. By intrathoracic inoculation of pneumococci, Talamon,[176]* in eight out of twenty rabbits, Weichselbaum[190] rarely, Gamaleia,[73] in dogs and sheep always, obtained pneumonic lesions, some of which were described as diffuse and lobar in type. With the pneumobacillus, Friedländer,[71]† in thirty-two mice and in one out of four dogs, Weichselbaum,[190] occasionally in mice and rabbits, obtained pneumonic lesions. In other similar experiments of these and many other observers, notably Kruse and Pansini,[106] Fraenkel,[67] Salvioli,[157 158] Foa and Rattone,[68] Klein,[101] Sternberg,[172] v. Besser,[19] and Silfast,[165] with pneumococci, streptococci, staphylococci, and the pneumobacillus, conducted on mice, rabbits, guinea-pigs, dogs, and horses, the inoculation failed to give rise to pneumonic lesions, although in the very susceptible animals a general systemic infection often ensued.

The *inhalation* of infectious material has been used chiefly as a test of the permeability of the normal lung to bacteria; but owing very largely to changes occurring in the virulence of the bacteria as a result of cultivation or the drying and pulverizing, and to the uncertainty as to how much if any of the infectious material ever reaches the air spaces, inhalation has proved a most uncertain method of infecting the lung. Pneumonic lesions usually circumscribed have, nevertheless, in exceptional instances, been noted, as in the researches of Buchner, Merkel, and Endelen,[29 54] Eppinger,[65] and Grammatschikoff,[75] with anthrax; of Friedländer,[71] Emmerich,[51]‡ and Chester,[36] with the pneumobacillus; and of Silfast,[165] with streptococci. Weichselbaum[190] failed to secure pneumonic lesions in his experiments with inhalation. The inhalation of the plague bacillus, as in the experiments of Batzaroff[11] and others, doubtless owing to the extreme virulence of this organism and the susceptibility of the animals used, has been remarkably successful in giving rise to the different types of plague pneumonia.

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reports the development of pneumonic lesions after intraocular inoculations with exudates which were not obtained in Veraguth's[183] similar experiments. In the course of my experiments, I have occasionally found at autopsy extensive consolidations of the lung, in which no bacteria or bacteria other than those inoculated were present, and which could only be attributed to chance or an intercurrent infection. A similar undetected infection may account for some of these unusual findings, especially in the early researches.

* Exudates were used for inoculation.

† Identity of cultures used is somewhat doubtful.

‡ Emmerich[52 53] claims to have invariably secured typical diffuse lesions in animals which had inhaled virulent pneumococci. His observations have never been corroborated; in fact, such inhalations have usually proved harmless.

By *tracheal injection* of the infectious material greater precision was given to the experiments and more definite results were thereby attained; but the virulence of the different bacteria in these experiments, as in those with inhalation, was a most important and variable factor. With pneumococci introduced in this way, Fraenkel[67]* rarely, Salvioli[159] in one rabbit and in two of four guinea-pigs, Kruse and Pansini[106] in possibly one of twenty-eight dogs, Tschistovitch[181] in seven of nineteen cats, and exceptionally in rabbits, obtained diffuse pneumonic lesions. Similar experiments of these and other observers, notably, Gamaleia,[72] Klein,[101] Guarnieri,[80] Griffiini and Cambria,[78] Talamon,[176] Lipari,[112] Welch,[191] Arustamow,[4] Müller,[125] Aufrecht,[5] Durck,[46] Coco and Drago,[39] and Carnot and Fournier,[33] with pneumococci, conducted on rabbits, guinea-pigs, cats, dogs, and sheep, failed to give rise to typical lesions, the inoculation proving either harmless or, as in very susceptible animals, giving rise to systemic infection, usually without, but in some instances, with small circumscribed lung lesions.

Patchy or circumscribed lesions have been occasionally induced by the tracheal injection of other bacteria, as in the experiments of Prudden and Northrup,[144] Orloff,[137] Fleck,[65] Laehr,[108] Durck,[46] Silfast,[165] and Beco,[13] with streptococci and staphylococci; of Lépine and Lyomet[111] with the typhoid bacillus; of Gamaleia[72] and of Tschistovitch[180] with the chicken cholera bacillus; and of Tschistovitch[180] with the bacillus of rouget du porc. Diffuse lesions following endotracheal inoculations have been reported by Gamaleia[72] with the bacilli of anthrax and chicken cholera, and by Bosc and Galavielle[25] with the micrococcus tetragenus. Finally, the various forms of plague pneumonia have been frequently induced by this method of inoculation. These are often hemorrhagic, usually bronchopneumonic, sometimes confluent and diffuse.

Experiments on the normal animal having given unsatisfactory results, attempts were made to render the lung more susceptible to infection by means of predisposants, which may be considered as acting chiefly upon the lung locally or upon the system at large. Many conditions, such as the inspiration of irritating substances, exposure to cold, trauma, fatigue, and disease, have long been recognized clinically as favoring the development of pneumonia in man. These and other conditions used as experimental substitutes for them have been extensively studied as to their effect *per se* on the animal and when combined with inoculation.

Previous Attempts to Induce Pneumonia in the Locally Predisposed Animal. The early researches of Heidenhain,[84] Arnold,[3] and Massalongo,[119] and the more recent work of Klipstein[102] and Beco,[13] in which the lungs of animals were exposed by inhalation or injection to various noxious substances in gaseous, liquid, or solid state, suffice to show that a series of changes largely desquamative, but often exudative, are effected in the tissues of the lung by these irritants.* That the changes thus induced in the lung tissue favor infection and the formation of lesions is well shown by the numerous experiments in which the injured lung has been directly inoculated through the trachea or the predisposed animal has been forced to inhale the infectious material. Such are the experiments of Buchner, Merkel and Enderlen,[29] and Muskatbluth[127] with anthrax; and of Prudden and Northrup,[144] Silfast,[165] and Beco[13] with streptococci and staphylococci; but the lesions in these experiments were usually circumscribed and bronchopneumonic in type. Typical diffuse lesions, however, Gamaleia[72] claims were always obtained when the injured lungs of resistant animals, such as the dog and sheep, were inoculated through the trachea with virulent pneumococci; in the normal lungs of these resistant animals the inoculation proved harmless, in the more susceptible animals this injury merely favored the development of fatal bacteriæmia without lung lesions.

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* More often with attenuated than with virulent cultures.[69]

As a result of *trauma* the lung tissues may be injured and thus predisposed to infection. If the integrity of the thorax is destroyed and the lung thereby exposed to external contamination, a wound infection accompanied by various disease processes of the lung, as well as of other tissues, may develop. If, on the other hand, the thorax remains intact, the trauma, acting purely as a predisposant, may give rise to changes in the lung, such as have been noted experimentally by Reineboth[146 148] and others,† which may favor the development of infectious material carried to the lung by the usual channels. In experimental pneumonia trauma is obviously a constant and possibly a determining factor.

Exposure to *cold*, long considered an all-important factor in the development of pneumonia, is now classed with trauma as a predisposant,‡ which, only in certain cases, may be a determining factor.§ Experimentally the effect of exposure to cold has been extensively studied. The changes brought about in the animal tissues have been attributed to the retention of deleterious products

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* Extensive lesions closely resembling those of acute exudative pneumonitis have been secured by such treatment without bacterial agency, but this is exceptional and the reports are confined to a few of the earlier observers.

† Traumatic pneumonia has also been extensively studied by Litten,[113] Meunier,[121] Reynaud,[150] Souques,[168] Gauthier,[73] and Schild.[161]

‡ Witness, for example, the table compiled by Comby:[40]

Bouilland attributed to cold			75	per cent.
Grisolle	"	"	20	"
Ziemssen	"	"	9	"
Jurgenson	"	"	4	"
Griesinger	"	"	2	"
Massalongo	"	"	0	"

§ Ruhemann,[155] however, considers the exposure to cold the exciting factor, and the presence of the bacteria the predisposing factor in the etiology of pneumonia.

of the body metabolism from diminished excretion (Eisenmann[50]), to reflex nervous action (Heymann[88]), and to the direct action of the cold on the tissues (Rosenthal[155]). These are very largely dependent upon the nature and extent of the exposure, upon the animal species used, and as shown by the researches of Nasaroff,[129] Durig,[47] and Lode,[115] upon the nutritive condition of the individual exposed. As a result of exposure the body temperature may be greatly influenced, as in the experiments of Eve,[59] who found that the experimental extremes compatible with recovery approximate those clinically observed in man, viz., 45° C. (113° F.) and 25 C. (77° F.). The marked fluctuations in blood pressure following exposure to either heat or cold, as in the experiments of Hegglin,[83] Grawitz,[76] Hermann,[87] Hadl,[81] and others, may give rise to hyperæmia, congestion, transudation, or even hemorrhage. Marked anæmia,[*] with reduction of both cells and hæmoglobin and with hæmoglobinuria, may develop, as in the studies of Chvostek,[37] Erhlich,[48] Grawitz,[79] Ebstein,[49] Fischl,[64] and Rheinboth and Kohlhardt.[149] Other cells of the body may undergo parenchymatous degeneration, as was noted by Lassar[110] and many others since his time. That these changes in the tissues resulting from exposure to cold predispose to many infections has been established by a great variety of researches, notably the early observers, Pasteur,[140] Wagner,[185] Ernst,[56] and Sawtschenko,[160] and the more recent writers, Chelmonski,[35] Lode,[114] Dieudonne,[43] Silfast,[165] Sanarelli,[159] Kisskalt,[99] and Reineboth and Kohlhardt.[149]

Owing to the anatomical structure of the lung these circulatory disturbances and the changes dependent upon them are especially well marked in this organ. Thus, in exposed animals, extensive lesions of the lungs were noted as early as 1862 by Walther,[183] and in 1870 by Wertheim,[192] and also recently by Durck.[45] The development of pneumonic infection in animals exposed to cold has been studied by means of the tracheal injection or the inhalation of infectious material, as in the experiments of Lode[114] and of Platania,[142] with the pneumobacillus and staphylococcus; of Silfast,[165] with streptococci; of Beco,[13] with staphylococci; of Carrière,[32] with attenuated pneumococci; and of Lipari,[112] with virulent pneumococci. In these experiments infection developed, and lesions, usually circumscribed or bronchopneumonic, were obtained more frequently than in normal animals. Lipari[112] alone reports definite results. Diffuse lobar pneumonia was obtained in all the exposed, but in none of the normal, rabbits of his experiments.

Circulatory changes, whether purely reflex and evanescent or associated with definite lesions and damage to the tissues, have been considered determining factors of local predisposition in the lung as in other organs and tissues. Attempts to demonstrate this experimentally have not been satisfactory: thus, Buchner[28] concluded that arterial hyperæmia was salutary; Kisskalt,[98,99] that arterial hyperæmia favored infection, but that stasis hyperæmia, as in tuberculosis, may act differently; Frenkel,[70] that sensory paralysis increased the susceptibility, while vasomotor paralysis increased the immunity, but neither had any effect in determining the general infection. Other observers, notably, Hermann,[86] Kasparek,[97] Meltzer,[120] Nekam,[130] Charrin and Ruffer,[34] and Roger,[153] have obtained results which suggested that innervation of a part favored the development of infection. These uncertain results are obviously to be attributed to many variable and indeterminate conditions, relating chiefly to the susceptibility of the animal, on the one hand, and to the nature and virulence of the bacteria on the other.*

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[*] The stimulating effect of mild exposure to cold has long been recognized, and the blood as well as other tissues may be greatly benefited by such exposure, as in the studies of v. Breitenstein,[26] Thayer,[177] Winternitz,[195] and of Speck.[169]

The normal lung, however, as compared with the other tissues and fluids of the body, is such an unfavorable environment for bacterial growth that a hyperæmia, with transudation by creating a more favorable soil, may be theoretically considered to favor infection in this organ. For experimental support of this, suffice it to refer to the above-noted predisposing action of irritation and trauma and of exposure to cold, the effects of which in the lung are largely due to circulatory changes.

The so-called *vagus pneumonias* have been studied by many of the early investigators, by Schou,[162] and recently by Müller[125] and by Esser.[58] Section of the vagus nerve, on one or both sides, has been frequently followed by the development of pneumonia, which has usually been of the patchy, bronchopneumonic type, though occasionally diffuse. The paralysis of the larynx, which facilitates infection of the lung by bacteria contained in the secretions of the upper respiratory passages and the circulatory changes set up in the lung, are the main factors in these experimental pneumonias. The results of these experiments prove that the method is uncertain, and, as compared with the direct inoculation of the lung with pure cultures of accurately determined bacterial species, such procedures are obviously crude.

Clinically, *previous disease processes*, especially those of the respiratory apparatus, are said to precede the development of pneumonia, and experience has shown that such inflammatory processes not only impair the protective resources of the parts, but afford favorable conditions for an increase of virulence in the bacteria present in the secretions. In Esser's[57] experiments the permanent changes left by healed inflammatory processes also favored the development of infection, and Aufrecht[6] cites statistics to show that the primary pneumonia predisposes to subsequent pneumonic infections. The predisposition effected by disease processes in other parts of the body, except possibly the heart, is obviously the result of an increased general susceptibility of the individual.

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* If the circulating blood is a favorable environment for the growth of the bacteria, a hyperæmia obviously favors infection; if unfavorable, retards infection. The experiments in this field have thus as yet added but little to our general theoretical knowledge.

PREVIOUS ATTEMPTS TO INDUCE PNEUMONIA IN THE SYSTEMICALLY PREDISPOSED ANIMAL. Many conditions influencing the system at large are well-known predisposants to infection. Some of these are clinically known to favor the development of pneumonia, and certain of the substances or conditions used as local predisposants undoubtedly act to some extent on the general system. Special methods of securing a systemic predisposition, however, have not been used in the experimental study of the etiology of pneumonia, except indirectly by Kaminer,[96] in his work on fibrin formation in the lung. Kaminer obtained pathological changes in the lungs of rabbits poisoned by phenylhydrazin in small repeated subcutaneous doses. In one animal a diffuse fibrinous lesion was found in the lung at autopsy. Bacterial examination failed to reveal micro-organisms.

SUMMARY OF THE RESULTS OF PREVIOUS RESEARCHES ON EXPERIMENTAL PNEUMONIA. General systemic infection of the animal by intravenous or by subcutaneous inoculation, whether practised on the normal or on the predisposed animal, has uniformly failed to give rise to pneumonic processes. Local infection of the lung from the inhalation of infectious material or by inoculation with virulent bacteria through the chest-wall, or, preferably, through the trachea, has, in some instances, been followed by the development of pneumonia. Practically all the various forms of primary acute exudative pneumonitis have thus been occasionally induced in predisposed and even in normal animals by many different kinds of bacteria. Of the different forms of pneumonia the bronchopneumonic or patchy has been most commonly incited; the typical diffuse lobar lesions have been secured with great difficulty and exceptionally.

It is evident and was early recognized that the nature and virulence of the bacteria inoculated were extremely important factors in each experiment; but it does not alone suffice to secure infection of the lung by means of highly virulent cultures, for this may, and does, as a rule, in susceptible animals, lead to a general fatal bacteriæma, which in nowise contributes to the development of local processes. A precise experimental control of subtle relationships between the virulence of the micro-organism, on the one hand, and the susceptibility of the animal, on the other, should therefore be sought. The virulence of the micro-organisms may be, and has been in many previous experiments, controlled by passing the cultures through animals of the species to be experimented upon. The susceptibility of the animal, however, has not been so definitely kept in hand. The various grades or conditions of susceptibility were not accurately determined and cannot be precisely compared, however suggestive in theory they may be.

THE WRITER'S RESEARCHES ON EXPERIMENTAL PNEUMONIA.

My studies were undertaken with a view of determining accurately the effect of increasing or diminishing the virulence of the incitant upon the development of pneumonic infection in normal animals and in animals whose susceptibility, local and systemic, was definitely increased. By using one micro-organism, the pneumococcus, and carefully controlling its virulence, and one animal species, the rabbit, whose susceptibility to pneumococcus infection was well known, it was hoped that comparison of the results obtained in a series of systematic researches would lead to more precise methods, and thus to more uniform and certain results.

TECHNIQUE. The media used for growing the pneumococci were made from meat infusion and were brought to a final reaction of less than 1 per cent. acid,* phenolphthalein being the indicator. Although glucose proved a valuable addition to the media, it was rarely used, as these cultures were very short-lived, probably on account of the acid developed. Ascites fluid was, in some instances, added to the broth. In tubes of pleuritic fluid, heated until semisolid, although still transparent, the pneumococcus stock cultures were kept at a temperature of about 10° in an accessible form, alive and virulent for several (eight or more) months. By this means the changes in the biological state of the micro-organism that usually attend repeated transfers were largely eliminated. It was, therefore, possible to work with the same unmodified races of pneumococci in all the experiments.†

Two races of pneumococci were used, one of low, the other of high virulence for rabbits. The first (A) was isolated from a fatal case of lobar pneumonia. The virulence of this organism may be approximately suggested by the fact that intravenously inoculated, 1 c.c. of a twenty-four-hour broth culture proved fatal; injected through the trachea this dose was harmless; subcutaneously inoculated, 0.5 c.c. of a twenty-four-hour broth culture induced an abscess at site of inoculation in two rabbits, and fatal septicæmia in two others inoculated from the same culture tube. The second (B) was obtained, through the kindness of Dr. Alexander Lambert, from the laboratory of the New York Health Department, where, by repeated serial inoculation in rabbits, it had been brought to a high virulence, 0.00001 c.c. of a twenty-four-hour serum broth culture at one time proving fatal to the average rabbit. This culture had, however, lost some of its virulence, for I found that although 0.1 c.c. of a twenty-four-hour broth culture intravenously inoculated excited severe reactions in rabbits, these were not always fatal. Owing to the previous adaptation of this race to rabbits, the potential strength of the culture was perhaps greater than was represented by my figures.

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* A reaction of 0.5 per cent. acid, which Dr. T. C. Janeway in some unpublished experiments has found to be an optimum, was in most instances used.

† For a more complete account of this method and media, see the Proceedings of the New York Pathological Society, April, 1903.

The inoculations were made with a Koch syringe into the ear vein or through the soft parts between the tracheal rings into the lumen of the trachea, which had previously been exposed by an incision through the skin and fasciæ. By careful technique in operating infection of the wound was avoided. The culture fluid was directed to the left lung by elevating and tilting the animal, but forced inspirations of the fluid carried it, in some instances, to the right as well as to the left lung. At the autopsies cultures and smears were usually made from the heart blood, trachea, and liver; in addition, the pleuræ were often, the spleen and kidney sometimes, examined. The smears were stained by the Welch[191] method for staining the capsules and also by the newer methods recommended by Hiss.[90] The lungs were distended with alcohol and all the specimens were hardened in this fluid. Sections of the lung, liver, spleen, and kidney were stained and examined for bacteria by the Gram-Weigert method. Other methods were also used in special instances, and by some of these, as yet not carefully determined, capsules could be demonstrated on the pneumococci in the sections of the lesions.

SCOPE OF THE EXPERIMENTS ON NORMAL AND PREDISPOSED ANIMALS. Intravenous, subcutaneous, and intrathoracic inoculations with pneumococci of varying grades of virulence were made in normal and in predisposed animals, with a view of retesting and corroborating the results similar methods had given in other hands. A number of tracheal injections with pneumococci of varying degrees of virulence were made in normal animals with the same object in view. The series of researches on predisposed animals with tracheal injections were thus accurately controlled. The predisposition was secured in three ways: the systemic susceptibility was increased by a chronic phenylhydrazin poisoning; the lung was locally injured by exposure to severe cold; and finally, by combining the two methods, a predisposition both local and systemic was obtained. In sets[*] of parallel experiments the effect of these forms of predisposition upon the development of pneumonic infection was studied by the tracheal injection of pneumococci of low and of high virulence.

ATTEMPTS TO INDUCE PNEUMONIA IN THE UNINJURED OR NORMAL RABBIT. *Subcutaneous*, *intravenous*, and *intrathoracic*[†] inoculation of normal animals with pneumococci of varying grades of virulence failed to give rise to exudative pneumonia. *Tracheal injection* of these organisms, however, yielded variable results. Pneumococci of low virulence when injected through the trachea had practically no effect on the lung and were rapidly disposed of. More virulent organisms incited varying, but for the most part small, central areas of exudative pneumonitis: of seven animals inoculated by the trachea, four died, and in two of these typical and extensive lesions of diffuse pneumonitis were found at autopsy. Pneumococci of still greater virulence injected through the trachea of five normal rabbits incited fatal bacteriæmic infections, with small areas of central bronchopneumonitis in but two. Thus in my experiments on normal animals, as in those of other observers, the diffuse lesions of exudative pneumonitis were rarely incited, and only when pneumococci of just the requisite grade of virulence were injected through the trachea; higher grades inducing fatal bacteriæmias, lower grades proving harmless.

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[*] Each set comprised three rabbits, not including the controls.

[†] Of fifteen normal rabbits, four cats, and one guinea-pig, inoculated through the right chest-wall, one cat developed a typical but small area of diffuse pneumonitis. The lungs of the other animals were comparatively free from lesions, although all the rabbits and the guinea-pig died, and local processes were found in the pleura and pericardium.

ATTEMPTS TO INDUCE PNEUMONIA IN THE POISONED OR SYSTEMICALLY PREDISPOSED RABBIT. In order to determine the effect of increasing the rabbit's systemic susceptibility upon the development of pneumonic infection, studies were made with intravenous inoculation and with tracheal injection of pneumococci of high and of low virulence on animals previously poisoned with phenylhydrazin hydrochlorate. As brought out by many researches, notably those of Heinz,[85] Kaminer,[96] Mya and Sanarelli,[128] and Lubarsch,[116] this drug in rabbits, besides many interesting but for the present purposes unimportant structural changes in the blood elements, gives rise to severe grades of anæmia of a secondary pernicious type with hæmoglobinæmia, hæmoglobinuria, and albuminuria. Various stages of parenchymatous degeneration and an œdematous condition of the tissues are also to be found in such animals.

Six rabbits previously poisoned by the repeated subcutaneous administration of phenylhydrazin in small doses were divided into two sets and injected through the trachea with pneumococci of low and of high virulence, respectively. All died in from twelve to fifty-six hours of a general bacteriæmic infection, and the only pneumonic lesion found was a small patch of exudative pneumonitis in the rabbit which lived fifty-six hours. The development of rapidly fatal general infections with little or no lung lesion in these poisoned animals, whether inoculated in the ear vein or through the trachea, and whether cultures of high virulence or of low virulence were used, shows that such rabbits are even less favorable subjects for the experimental incitement of diffuse lesions than the normal animal. The studies were then directed to the effect of increasing the local susceptibility of the lung.

ATTEMPTS TO INDUCE PNEUMONIA IN THE INJURED LUNG OR LOCALLY PREDISPOSED RABBIT. An increase in the susceptibility of the lung without much disturbance of the system at large is obviously best accomplished by means of local irritation. Such methods have been so exhaustively studied by others and have proved, in the rabbit at least, so consistently unsatisfactory as a means of obtaining diffuse lesions that exposure to cold—another method of rendering the lung more susceptible—was adopted.

The animals were tied to trays and placed in ice baths at temperatures of 7° C. to 12° C. for five minutes. Immediately after the bath the animals were taken from the trays and wiped with towels. After these exposures various changes were noted. In the lungs large and small areas of hyperæmia and congestion, occasionally small hemorrhagic extravasations were found. The rectal temperature fell for a period of five, ten, or even twenty minutes after the bath; the lowest observed in animals which recovered was 26.5° C.

A general bacteriæmic infection without lung lesions followed the intravenous inoculation of these animals with pneumococci of varying degrees of virulence, and the exposure of normal rabbits to cold when combined with the tracheal injection of pneumococci also proved an inadequate means of securing definite pneumonic lesions. A study of the effect of combining these methods was therefore made.

ATTEMPTS TO INDUCE PNEUMONIA IN THE SYSTEMICALLY AND LOCALLY PREDISPOSED RABBIT. Intravenous inoculation as heretofore failed to give rise to local processes in the lung and similarly the tracheal injection of the more virulent pneumococci incited but little reaction* in the lungs of these animals, all three of which died of a general infection. With pneumococci of comparatively slight virulence the tracheal injection of these emaciated and exposed rabbits gave rise to extensive and diffuse lung reactions, which were considered typical and comparable to the lobar pneumonias of man in two of the three animals of the experiment.

Of these three rabbits: one died in twenty hours and developed slight bronchial reactions similar to those found in the animals injected with the more virulent organisms; another died in thirty hours, and diffuse lesions in an early stage involved the upper portion of the lower and the lower portion of the upper left lobes; the third lived four and one-half days, and at autopsy typical red and gray hepatization, macroscopically and microscopically, were found in the upper left lobe.

SUMMARY OF THE RESEARCHES ON NORMAL AND PREDISPOSED ANIMALS. It was thus finally possible to approximate at least the balance of conditions as to the virulence of the bacteria on the one hand and on the other the special degrees of local and systemic susceptibility of the animal necessary for the development of typical diffuse lesions of the lung. With an increased susceptibility of the animal pneumococci of low virulence only could be used. Moreover, both the local and systemic susceptibility of the animal in varying degrees must be increased. Such a fine balance of conditions, it is obvious, might not always be easily obtained, and the practical solution of the problem had to be sought along other lines.

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* One rabbit of the set of three lived sixty hours and showed more marked lesions than the others which died in twenty-four and thirty-six hours. None of the lesions were typical.

Heretofore, in the experiments of others and in my own described above, the predisposition was secured by methods which increased the susceptibility of the animal to infection. In the lungs of such animals organisms of sufficient virulence to incite extensive lesions gave rise to a rapidly fatal bacteriæmia, and the reaction of the body tissues was thereby generalized or inhibited, so that the local processes failed to develop. The attempts of others to obviate this early development of a bacteriæmic infection by selecting less susceptible animals for experimentation having proved uncertain and as yet impracticable, I sought a method of rendering the rabbit less susceptible to such infection. As this could easily be accomplished by immunization, my studies were directed to this field of experimentation.

ATTEMPTS TO INDUCE PNEUMONIA IN THE IMMUNIZED RABBIT.

Preliminary Experiments. Two animals were immunized by the inoculation of non-virulent cultures of pneumococci. Their blood serum failed to agglutinate pneumococcus cultures in dilution of 1:1, and they died from the virulent tracheal injection in twelve and eighty hours. Two other rabbits were immunized by the subcutaneous inoculation of virulent pneumococci, which induced serious but not fatal local disease processes. Their blood sera agglutinated the pneumococcus cultures in dilution of 1:1, and they survived the tracheal injection. In the rabbit which died twelve hours after the tracheal injection, an early stage of an exudative pneumonitis involving the whole left lung was found at autopsy. Similarly extensive and diffuse lesions of a later stage were present in the animal which lived eighty hours. The other two rabbits recovered from the effects of the tracheal injection and were killed on the third day. Lesions of a resolving diffuse exudative pneumonia involving large areas in one animal and small, more circumscribed areas in the other were found in the lungs.

Additional researches were divided into three sets of experiments, respectively, comprising: five immunized and two normal rabbits, four immunized and three normal rabbits, four immunized and two normal rabbits. Of the thirteen immunized rabbits injected through the trachea, but one died of the infection, and of the seven normal animals three recovered from the inoculation. Diffuse and typical lesions were incited in a considerable proportion of the animals, and the processes were more marked and more frequently found in the immunized than in the normal control animals; but the difference was not sufficiently definite, and it was evident that there were certain errors in the methods used. Obviously either the virulence of the pneumococci inoculated or the degree of immunization attained by the animals was at fault.

At first the immunization of the animals was thought to have been inadequate, but the fallacy in this was apparent on recalling the fact that many animals had died in the process of immunization, and the survivors used for the experiment, though often greatly emaciated, withstood the virulent tracheal injection. By means of a specially devised technique insuring accurate results* the blood sera of these animals was tested as to its agglutinative action on pneumococcus cells, and the results were compared with those obtained with other blood sera of better-known strength. Thus it was determined that the rabbits had attained an extremely high degree of immunization.

The cultures used for inoculation were of pneumococci grown in exudates taken from animals dying of pneumococcus infection and diluted with broth in about equal proportions. Inoculation with such cultures often failed to kill the normal rabbit, whereas cultures of this pneumococcus in broth or in normal sera by tracheal injection or by intravenous inoculation in much smaller doses ($\frac{1}{400}$ c.c.) invariably proved fatal. A similar loss of virulence in organisms grown in immune sera was noted by Metschnikoff,[122] and that this loss in virulence is only apparent, not real, was determined by the researches of Metschnikoff's pupils, Isaeff[94] and Arkharow,[1] and also by the recent studies of Walker.[186] The lack of virulence in the tracheal injections of my experiments was therefore attributed to the presence, in the exudates used for culture media, of protective substances, which, in the lungs of the immunized or even of the fresh normal rabbit, became active. In this way an effect was obtained comparable to a lack of virulence not actually existing in the pneumococci.

It thus became evident that in these researches, as compared with the first preliminary experiments, the conditions essential to the development of pneumonic processes in the rabbit had unwittingly been altered by the above-noted errors in technique; so much so in fact that the necessary balance for the formation of typical diffuse lesions was present in a majority but not in all of the immunized animals.

Final Experiments. By avoiding what in the previous experiments seemed to be the chief faults, namely, a too high degree of immunization in the animal, and a neutralization of the virulent inoculation, more complete results were expected and obtained in a final experiment on eleven immunized† and five normal rabbits.

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* Fully described in a paper published in the Journal of Medical Research, 1903, vol. x., No. 2.

† Eight normal rabbits in the process of immunization received: *March* 6, 1903. 1.5 c.c of a salt solution suspension of pneumococcus cells dissolved by normal rabbit bile: subcutaneous. *10th*. 5 c.c. sterilized broth culture of pneumococci: intravenous. *12th*. 2 c.c. of the bile solu-

March 6, 1903. The eleven immunized and five normal control rabbits were tracheally injected with 1 c.c. of a culture of the extremely virulent pneumococci grown in normal rabbits' serum diluted with broth.

Of the five control animals, three died in forty-eight hours without lung lesions; a fourth lived four days, and a small area of exudative pneumonitis was found at autopsy. The fifth was dying on the fifth day, when it was killed, and a similar lesion of the lung was found in this animal.

Of the eleven immunized animals none died; but a few were seriously ill for twenty-four to thirty-six hours. The first set of eight were killed on the third day; the second set of three on the fourth day after the tracheal injection. The various lesions of acute diffuse pneumonitis involving considerable areas of the left lung were present at autopsy. The smallest lesion found in any of these rabbits comprised at least a quarter of the lower lobe. In one animal, however, the entire left lung, with the exception of the lowermost tip, was solid. Cross-section showed the granular appearance seen more markedly in the human lung.

SUMMARY OF THE EXPERIMENTS ON IMMUNIZED ANIMALS. It is evident from these experiments that in the lungs of immunized rabbits virulent pneumococci do not give rise to an early general infection, but are confined to the lung, where, if the animal be not too highly immunized, they develop, inducing disease processes comparable to the lobar pneumonia of man. In the experimental control of these conditions under which diffuse lesions may be obtained, there are but two chief variable factors to be considered—the virulence of the micro-organism on the one hand, and the degree of immunization on the other—both easily and accurately determined by the ordinary routine methods of the modern laboratory.

GENERAL CONSIDERATIONS.

THE HISTOLOGY OF THE EXPERIMENTAL PNEUMONIAS. The type of inflammation in all the experimental lesions obtained with the pneumococcus was purely exudative and diffuse, usually with abundant formation of fibrin. All stages in the development of the reactions were present in the different lesions, and it was impossible to draw any sharp lines of distinction between the simple bronchitis and the bronchopneumonic reactions, or between the bronchopneumonias and the diffuse lobar lesions. The one merged gradually into that of the other, although the types were easily distinguished.

The leukocytes were usually numerous and particularly prominent

tion of pneumococcus cells: subcutaneous. *26th.* 1.5 c.c. of clear salt solution extract of pneumococcus cells: intravenous.

Three normal rabbits in the process of immunization received: *March* 2, 1903. 3 c.c. of a salt solution suspension of sediment from pneumococcus growth in glucose broth; intravenous. *3d.* 3 c.c. subcutaneous.

in the early stages of the lesion. The exfoliation of epithelium also occurred early in the process, but the desquamated cells were relatively more numerous in the later stages. Few fibrin fibrils could be found in the very early stages, but granules were often abundant. As has been noted by Kohn,[103] Hauser,[82] Bezzola,[21] and others, the fibrin developed and was more abundant in the early stages along the walls of the air spaces, and in places the fibrils could be traced from one alveolus to another. In the more advanced lesions the fibrin formation was most marked in the centre of the exudate, a clearer zone lying next the alveolar wall.*

The pneumococci were present, often in large numbers, in all the early stages of the lesions. The cocci were for the most part outside the cells. In resolving lesions the bacteria were often absent, even though large portions of the lung were involved. This was particularly noticeable in the lesions which were found in the immunized animals. Areas of irregular development gave to the lobar lesions during the early stages a patchy appearance. These areas may or may not correspond with the lobule of the lung; certainly they were not as distinct as the lobular patches present in human lobar pneumonia, nor could the intralobular structure described by Bezzola[21] and Ribbert[151] be definitely made out. The lung of the rabbit doubtless offers certain differences in the anatomical structure or arrangement of its lobules which may possibly explain these slight discrepancies. Furthermore, the posture of the animal doubtless influences the absorption and accumulation of exudates in the lung and thus, to some extent, the character of the lesion.

THE DEVELOPMENT OF EXPERIMENTAL PNEUMONIA. It is obvious that the development of localized disease processes in the lung, as elsewhere, is determined by conditions referable either to the infecting micro-organism or to the animal infected. The infecting micro-organisms are extremely susceptible to environmental influences and thus exhibit considerable biological variation of both species and race. The biological character of the bacterial species as regards the peculiarities of growth and the elaboration of toxins and the special adaptation of the individual or race to the animal infected, commonly though inadequately expressed by the term virulence, are thus essential determining, but extremely variable factors in the development of all infections. On the other hand, the animals infected, within certain variable limits, afford favorable or unfavorable environments for the incitants of infection; in short, the animals are in varying degrees susceptible of infection.† This susceptibility may be local as affecting certain tissues or parts of the animal or it may be systemic. When the bacterial incitant is extremely virulent or the animal very susceptible a systemic infection is induced, but when the bacterial incitant is less virulent or the animal only partially susceptible, a local infection is induced.

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* In distended or inflated lungs an artefact is often produced which should not be confused with these appearances.

† An important and co-operating factor intimately associated with the susceptibility of the animal is the chemotaxis. In animals very susceptible to certain infections it has been shown experimentally that, with extremely virulent cultures of the incitants, the chemotaxis is negative. In less susceptible animals or in immunized animals or with less virulent incitants the chemotaxis is in varying degrees positive.

The morphological character of the disease processes depends in part upon the grades of susceptibility in the animal tissues, but chiefly upon the nature and virulence of the bacterial incitants, which, as noted above, are extremely variable. Different races of the same bacterial species thus often give rise to very different types of lesion in different or even in the same species of animal. Similarly, according to the degree of specialization necessary in the bacterial incitant, the different types of lesion may each be induced by a large or a small number of bacterial species or even by only one species, as in the so-called specific lesions. For example, in the lung, many different kinds of bacteria give rise to bronchopneumonia, but few to diffuse lobar pneumonia, and only one, the tubercle bacillus, to a specific productive necrotic process called tuberculosis.

Owing to the special anatomical arrangement of the epithelial, vascular, and lymphatic tissues of the lung, and to the physiological or pathological adaptation of these tissues, the lung surface acts, to some extent, similarly to the skin and mucous membrane as a barrier to infection, yet is peculiarly fitted not only for the rapid absorption and elimination of toxic material, but for the rapid diffusion of such material and the accumulation of exudates. The problem of infection in the lung is thus obviously complicated, and the relationship between the above-cited essential factors of infection more subtle than in other parts of the body. For most bacteria the normal lung is unfavorable, and similarly for the bacteria commonly found in pneumonic lesions the lung, as compared with other tissues, is, in most animals, a less favorable environment; thus for infection of the lung special adaptation or virulence of the bacterial excitant is essential. If this virulence be too great, the micro-organisms gain early access to and develop more rapidly in the other more favorable tissues of the susceptible animals. If this virulence be moderate, localized processes are incited in the lung, the surface of which, acting as a barrier to infection, prevents the invasion of the more susceptible tissues until the animal becomes, in a measure, immunized or the organisms acquire the requisite virulence for systemic infection. For the development of extensive diffuse lesions of the lung a relatively extreme adaptation or virulence of the incitant is obviously essential; thus these lesions rarely develop in animals very susceptible to the infection. Furthermore, bacteriæmias, whether temporary or terminal, are apt to complicate such disease processes. A relative systemic insusceptibility, whether natural to the animal species or acquired by the individual,* is, therefore, an extremely important factor in the development of lobar pneumonia. For the formation of circumscribed or patchy lesions of the lungs less specialization or virulence of the incitant is required; thus the protective mechanism of the lung is usually an efficient barrier shielding the more susceptible tissues from infection, and bacteriæmias are comparatively rare. Occasionally, however, as in susceptible animals infected with incitants which possess or quickly attain a high virulence, a systemic infection supersedes the localized pneumonic lesion. Plague pneumonia is an apt illustration of the development of bronchopneumonia under these conditions, which, except for the lack of systemic insusceptibility, are the same as give rise to lobar pneumonia. Thus it is that in bronchopneumonia and in lobar pneumonia similar etiological conditions in slightly varying relationship give rise to slightly varying lesions differing only in type.

THE PNEUMONIC PROCESS IN MAN IN THE LIGHT OF THESE EXPERIMENTAL RESEARCHES ON ANIMALS. All grades of reaction from the idiopathic lung congestions (Maladie de Woillez) to the diffuse lobar pneumonic lesions may be induced by pneumococci in the lung of man. In these the different races of pneumococci exhibit wide variations in virulence. Carrière[32] found attenuated pneumococci in the lung congestions, whereas it is well known that those isolated from lobar lesions are usually extremely virulent. Eyre and Washbourn[61] tested four stocks of pneumococci: one from the sputum of a healthy person, three from pneumonia cases. The pneumonia cultures became excessively virulent by passing them through from eight to eleven rabbits, 0.00001 loop proving fatal in rabbits. The sputum culture was passed through forty-three rabbits before 0.001 loop was fatal, and fifty-three before 0.00001 loop proved fatal. The subsequent observations of these authors confirm the above-noted results.

It is well known that, relative to other species, man is more resistant† to pneumococcus infection. However, the resistance offered by different races of men varies greatly. Billings,[22] from the census report, found that the negro is markedly susceptible to pneumonic infection. Marchoux[118] reports an epidemic of pneumococcus infection of a bacteriæmic type occurring in a body of French colonial negro troops. Although disseminated lesions were present, well-developed pneumonias were comparatively rare. Kolle[104] noted a similar epidemic among the negroes of South Africa, but lesions were found in the lungs of some of these cases. Brodie, Rogers, and Hamilton[27] studied two epidemics of severe general pneumococcus infection, characterized by rhinitis and gastrointestinal disturbances, occurring in the Kaffirs. Pneumonic lesions were rare. Tostivant and Remlinger[183] describe the marked susceptibility of certain Arab tribes to pneumococcus infection and the difference in the lesions induced.

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* This systemic insusceptibility may be acquired by individuals normally susceptible, in the early stages of the infection which may for a time be confined to the air spaces where the exudates collect; thus lobar pneumonia is occasionally induced in very susceptible animals. Such a fine balance of conditions is for the present at least beyond experimental control.

† The presence of the pneumococcus in the sputum of health and in many of the disease processes of the nose, throat, and ear suggests that more or less specific resistance may be developed at times in some if not in many individuals. By means of a special technique I have obtained agglutinin and precipitin reactions with the blood serum from certain animal species not usually susceptible to pneumococcus infection, and with the normal human sera tests these reactions were more marked and developed in higher dilutions. (Journal of Medical Research, 1903, No. 2, vol. x.)

Aside from racial susceptibility, the individual at different ages and under different conditions offers striking analogies, in some instances to the susceptible, in others to the resistant, animal. In general, the newborn and the infant are remarkably susceptible to infection. At this age lobar pneumonias are rare; infection of the lungs with pathogenic bacteria gives rise to the bronchopneumonic type of lesion. Here, then, is a direct analogy to the susceptible animal. In the adult, as in the resistant or immunized animal, lobar lesions are more commonly found in the primary pneumonias; but, on the other hand, the adult may be rendered in varying degrees susceptible by other disease processes, and exudative pneumonitis developing under these conditions, the so-called secondary pneumonia, is more apt to be of the bronchopneumonic type.

It has long been recognized clinically that in the lobar pneumonias of man there is no definite relation between the extent of the lesion and the gravity of the infection upon which a prognosis may be safely based. This is even more pronounced in the experimental pneumonias in animals, and, as shown by the researches on animals, is due to the fact that extensive lesions may be incited by virulent infections when confined to the lung without seriously endangering the life of the individual; whereas less extensive lesions are often followed by general infections which terminate fatally. Thus the lesions in the fatal lobar pneumonias of old people are often small, sometimes unrecognized; whereas the lungs of a robust individual with good protective resources may be extensively involved, and yet recovery take place. As suggested by the researches on animals, the generalization of the infection is the real danger. Upon the determination of this only can a prognosis be safely based.

It is therefore evident that the various phenomena of pneumococcus infection observed in animal inoculation also occur in man. The rule of one is, however, the exception of the other; thus, general infections, except as transitory or terminal conditions complicating the local processes are comparatively rare in man, but common in the ordinary laboratory animal.

SUMMARY AND CONCLUSIONS.

As a result of the numerous and varied researches of other observers it has been determined that the bronchi and lung under normal conditions are practically free from micro-organisms; that the secretions of the upper respiratory tract in both health and disease often harbor the bacteria commonly found in pneumonia, namely, the pneumococcus, the streptococcus, the staphylococcus, and the pneumobacillus; that the incitants of pneumonia may be carried to the lung by the lymph channels, inducing an interstitial pleuropneumonitis; or by the bloodvessels, giving rise to secondary metastatic processes; or, as is usual, by the air-passages, inciting the various lesions of exudative pneumonitis, of which two main types, the bronchopneumonic and the diffuse lobar, are recognized; and, finally, that the bronchopneumonic lesions, whether arising in man or induced experimentally in animals, may be incited by a great variety of bacteria, most frequently by the pneumococcus or the streptococcus; whereas, comparatively few species of bacteria give rise to diffuse lesions in animals, and in man practically but one species, the pneumococcus, ever attains the necessary specialization for the incitement of lobar pneumonia.

In the researches of others patchy or circumscribed lesions comparable to the bronchopneumonia of man, have been induced experimentally with comparatively little difficulty. Previous attempts to induce diffuse lobar lesions in animals, though successful in a few exceptional instances, have failed to determine the exact conditions under which the lesion develops and offer no reliable method of securing typical pneumonic processes.

By means of accurately controlled series of experiments which allowed of precise comparison, it was possible in my researches to determine the effect of increasing or diminishing the virulence of the incitant, the pneumococcus, in systemically predisposed, in locally predisposed, and in both systemically and locally predisposed animals. These experiments show that the incitement of diffuse lesions in the normal rabbit is extremely uncertain, and only possible in the predisposed rabbit when both the general and local susceptibility are increased and when organisms of comparatively low virulence are used. Thus, and owing chiefly to the fact that the lung surface acts as a barrier to infection, the development of acute exudative pneumonitis offers an especially clear example of the nice balancing of the essential conditions determining infection. These conditions are, on the one hand, the specialization or virulence of the incitant, and, on the other hand, the animal susceptibility, both local and systemic. Organisms of low virulence induce evanescent bronchial reactions; more virulent organisms by a local infection, give rise to the more typical bronchopneumonic lesions; while organisms of still greater virulence, if confined to the lung, incite diffuse processes of the lobar type, but if not so confined and bacteriæmic infection occurs, the lung lesions are less marked and of the bronchopneumonic type. The extremely fine balance of these conditions essential to the formation of lobar lesions in normal as well as in predisposed animals is as yet for practical purposes beyond experimental control.

Finally, as a result of these systematic researches on normal and predisposed animals, an entirely new procedure was adopted: the preliminary immunization of the rabbits, so that extremely virulent cultures of pneumococci can be used without giving rise to bacteriæmic infection. The experiments with this procedure showed that diffuse exudative lesions comparable to the lobar pneumonia of man may be incited experimentally in the immunized rabbit; and that in securing this result there are but two chief variable factors, the virulence of the incitant and the immunization of the animal; both easily and accurately controlled by the routine technique of the modern laboratory.

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HEREDITARY ŒDEMA.

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Although the influence of heredity as a factor in the production of certain forms of œdema, not of cardiac or renal origin, was mentioned by Quincke in 1882, it was not until 1888, when Osler published the details of a case, that the subject attracted general notice in this country. This was probably due, first, to the eminent